Recent Vaccination Improves the Early Control of Virus in SHIV Infection but not the Clinical Outcome

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The United Nations Acquired Immunodeficiency Syndrome (UNAIDS) organization reported that, at the end of 2007, approximately 40 million people were living with human immunodeficiency virus (HIV) [1]. Of these, 25.8 million (64%) were located in the developing countries of sub-Saharan Africa (Fig. 1). Since the beginning of the epidemic over 25 million people have died of the complications occurring in late stage HIV [1], when acquired immunodeficiency syndrome (AIDS) manifests itself. The best hope the world has to control this epidemic is the development of efficient vaccines.

We have been working to understand the dynamics of virus and immune response within the host for different experimental vaccines. How do they affect the early viral growth kinetics [2]? What are the dynamics of the immune response [3-5]? We have been collaborating with Merck & Co, Inc., to analyze its experimental data on a $CD8^+$ T-cell inducing vaccine. Our objective was to shed light on the effects of the time that elapses between vaccination and infection on the performance of the vaccine.

Twenty-eight rhesus macaques were given a vaccine-boost protocol, and groups of four macaques were then challenged with virus at 1, 3, 6, 12, and 24 weeks after the boost. We used statistical methods to characterize the kinetics of viral load, $CD4^+$ and virus-specific $CD8^+$ T-cells. We found that all vaccinated animals showed an increase in $CD8^+$ T-cells compared to control animals, but that the number of virus-specific $CD8^+$ T-cells had an exponential decay between 1 and 12 weeks following vaccination (Fig. 2). However, the viral and T-cell kinetics over the first 2 weeks differed between the vaccinated groups (Fig. 3), with more recent vaccination improving the early control of virus. Interestingly, the rates of virus-specific $CD8^+$ T-cell expansion were greater in animals having higher viral loads at 1 week.

Differences in time of challenge since vaccination did not lead to differences in the clinical outcome for vaccinated animals. However, the dynamics of the virus after recent vaccination was qualitatively different from later challenges and these dynamics of early viral load seems to have a role in virus-specific $CD8^+$ T-cell generation.

These studies are important in thinking about what will be the correct protocol for vaccination, boost, and revaccination once an effective HIV vaccine is developed.

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[1] *UNAIDS/WHO AIDS Epidemic Update,* UNAIDS/WHO, Geneva (2007).
[2] M.P. Davenport, et al., *J Virol,* **78,** 10096-10103 (2004).
[3] M.P. Davenport, et al., *J Virol*, **79,** 10059-10062 (2005).
[4] M.P. Davenport, et al., *J Acquir Immune Defic Syndr,* **41,** 259-265 (2006).
[5] M.P. Davenport, et al., *Immunol Rev,* **216,** 164-175 (2007).

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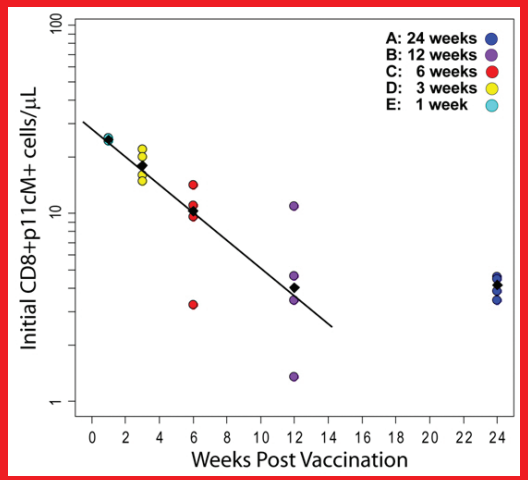

Fig. 2. Decay and plateau of virus-specific $CD8^+$ T-cells after vaccination and before viral challenge. Individual animals (colored circles) and group median (black diamonds) are shown. In the vaccinated and boosted groups, the animals' virus-specific $CD8^+$ T-cells drop monotonically with time between weeks 1 and 12.

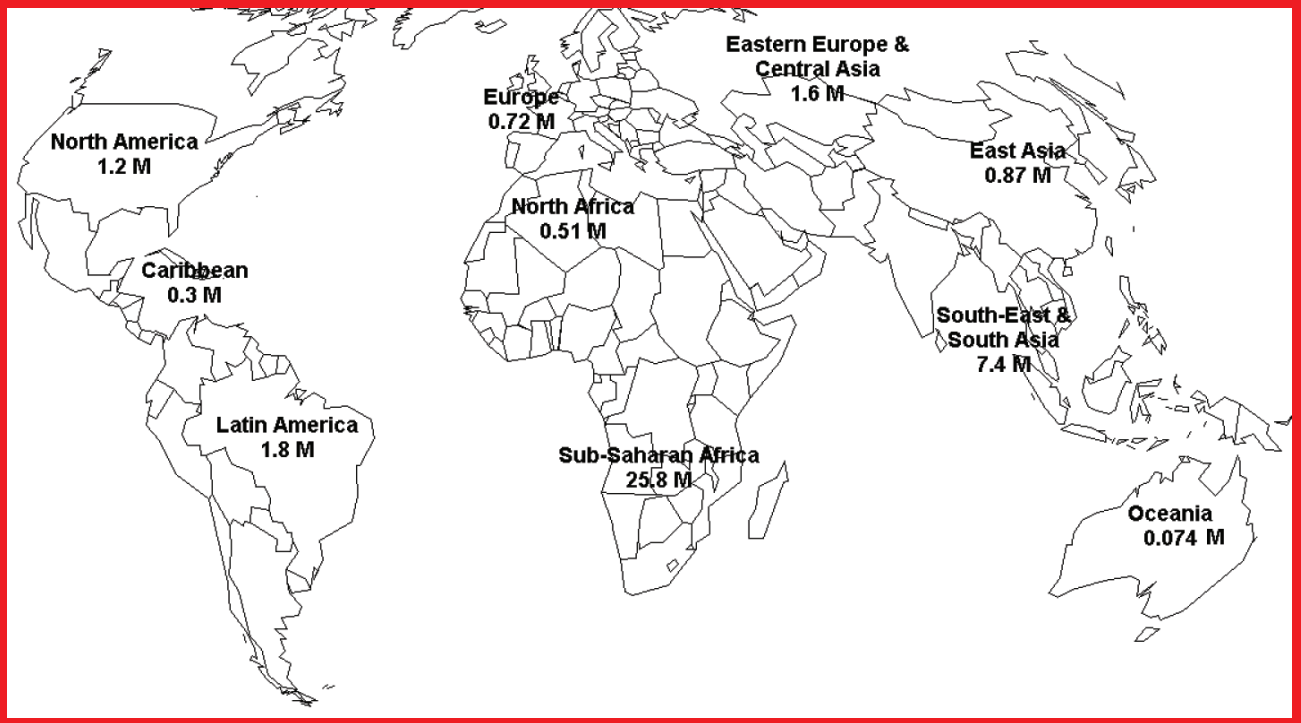

Fig. 1. **The burden of HIV.** *Approximate number and geographical distribution of HIV-infected people in the world.*

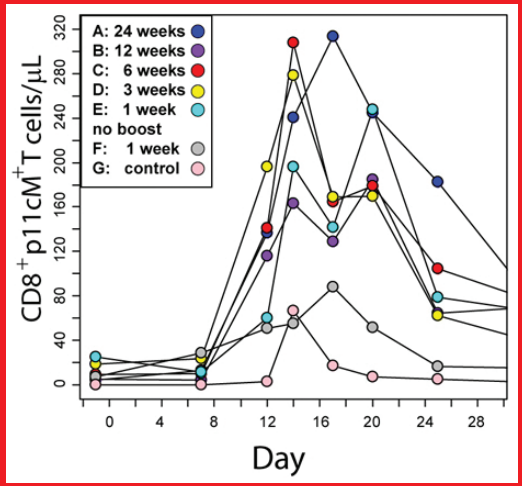

Fig. 3. Acute infection profile of virus-specific CD8⁺ T-cells differs by challenge time (profiles are averaged over the four macaques in each group).